*al.* do not teach specifically that monomers are separated from dimers and/or multimers of the monomers, the method would inherently possess this property. Further, since the method of Yang *et al.* is a method of purifying proteins, and the limitations recited in the instant claims are drawn to a protein purification method, the Examiner contends that one skilled in the art would expect that the identical protein purification methods would function in identical ways. Thus, absent evidence to the contrary, according to the Examiner, the method of Yang *et al.* would be effective to purify monomers from dimers and multimers of the monomers, and would result in the same levels of purity. This rejection is respectfully traversed.

Anticipation requires that all of the elements and limitations of the claims be found within a single prior art reference. There must be **no difference** between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) (emphasis added). Absence from a cited reference of any element of a claim negates anticipation of that claim by that reference. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984).

In the event that a reference does not explicitly teach all elements of a claim, anticipation can be shown by inherency. To establish inherent anticipation in the absence of an express disclosure, two distinct showings are required: first, the inherent characteristic must **necessarily** be present in the prior art reference; **and** second, such characteristic would have to have been **recognized** by a person of ordinary skill in the art at the time. *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995); *Continental Can Co. USA Inc. v. Monsanto Co.*, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

Substantial uncertainty regarding the existence of a product in the prior art, *i.e.*, uncertainty as to whether the inherent characteristic **necessarily** flows from the teaching of the prior art reference, is enough to preclude anticipation. *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983; *Bristol-Myers Co. v. USITC*, 15 USPQ2d 1258 (Fed. Cir. 1989).

The second prong of the test, *i.e.*, recognition of the inherent feature, is based on the principle that unappreciated events or things are, by definition, not known to the public, and therefore, should not anticipate under 35 U.S.C. § 102, which requires that subject matter relied on as anticipatory be disclosed in a manner sufficient to place it in possession of the public. *See, Akzo N.V. v. USITC*, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986); *In re Samour*, 571 F.2d 559, 197 USPQ 1 (CCPA 1978). Thus, it would appear that a prior, but unappreciated, existence of a product might inherently anticipate **only if** there is a reasonable likelihood that a person of ordinary skill at the time prior to the invention could have discovered the product without specific guidance, *e.g.*, without the benefit of the applicants' teachings, or teachings of a secondary reference. Moreover, it is well established that an accidental or unwitting duplication of an invention cannot constitute anticipation. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978).

The claimed invention is directed to a method for separating polypeptide monomers from a mixture comprising (a) said polypeptide monomers and (b) dimers or multimers of said polypeptide monomers or (b) both dimers and multimers of said polypeptide monomers. This method consists essentially of applying the mixture to a cation-exchange or anion-exchange chromatography resin in a buffer, wherein if the resin is cation-exchange, the pH of the buffer is about 4-7, and wherein if the resin is anion-exchange, the pH of the buffer is

about 6-9, and eluting the mixture at a gradient of about 0-1 M of an elution salt, **wherein the monomer is separated from the dimers or multimers or both present in the mixture and the separated monomer has a purity of greater than 99.5% and the monomer yield is greater than 90%.**

The Section 102 rejection based upon Yang *et al.* must fail as a matter of law because Yang *et al.* do not disclose each and every element of the claimed invention.

The Examiner contends that Yang *et al.* teach method steps that are identical to the instantly claimed method, regardless of what type of molecule is sorted or purified, or what it is sorted or purified from. However, Yang *et al.* do not, in fact, teach the positive recitation in claim 1 of the stated result of the method steps, i.e., the monomer is separated from its dimers or multimers or both present in the mixture at the minimum purity and yields specified.

At the relevant time of filing the above application (June 1, 1998), the disclosure of Yang *et al.* would not have conveyed to the skilled practitioner in this field the above stated result, i.e., that monomeric proteins can be purified from dimeric and/or multimeric forms thereof and obtained in a yield and level of purity of such high degree utilizing the ion-exchange technique of Yang *et al.* In this regard, the Examiner is referred to the enclosed Declaration by Dr. Steven Cramer, a renowned expert in protein separations.

In paragraph 6 of that Declaration, Dr. Cramer states that one skilled in the chromatographic field would view Yang *et al.* in the context in which it is written. Ion-exchange chromatography is a common method for separating proteins, and Yang *et al.* merely utilizes this technique to carry out what would be expected in the art. Thus, Yang *et al.* are separating polypeptide monomers from other monomeric

forms thereof (such as differently glycosylated or post-translationally different immunoglobulins), or from totally different polypeptide monomers contained in the ascites and sera, or from dimers and/or multimers that may be naturally contained in ascites and sera. However, Yang *et al.* do not explicitly disclose separation of such monomers from **their own** dimers and/or multimers. The skilled artisan would not have believed as of June 1, 1998 that separation of monomers from their own dimers and/or multimers to produce therapeutically acceptable polypeptides could be accomplished at such high yield and purity by ion-exchange chromatography. Before the filing date of this application, the skilled artisan was using size-exclusion chromatography for this purpose. Yang *et al.* do not tell the skilled scientist that ion-exchange chromatography is the answer, since ascites and sera loaded onto the column are complex mixtures of components that do not necessarily contain such dimers and/or multimers. Dr. Cramer concludes by stating his opinion that one of reasonable skill in the art would not believe that Yang *et al.* discloses all stated features and elements of the claimed invention.

Further, Yang *et al.* do not show anticipation of the instant invention by inherency. As noted above, to establish inherency, the inherent characteristic must **necessarily** be present in the prior art reference **and** such characteristic would have to have been **recognized** by a person of ordinary skill in the art at the time. In the present case, Yang *et al.* do not meet either of these requirements for it to render the claimed invention inherent. More specifically, the protein loads utilized by Yang *et al.* in their chromatography would not allow one of reasonable skill in this field to reach the conclusion that purification of monomers from their dimers and/or multimers would be feasible, much less would necessarily flow from the disclosure of Yang *et al.* See paragraph 7 of the enclosed

Declaration by Dr. Cramer. Since uncertainty exists as to whether the inherent characteristic necessarily flows from Yang *et al.*, Yang *et al.* do not anticipate the present invention.

Moreover, the second prong of the inherency test requires that one of ordinary skill in the art at the time of the present invention would have appreciated or recognized the inherent feature, namely, that dimers and multimers could be separated from their own monomers and that such monomers could be obtained within the yield and purity levels recited in the claims. Clearly, no such recognition can be found or supported by Yang *et al.*

In paragraph 8 of the Cramer Declaration he states that one of ordinary skill in the field as of June 1998 would not have appreciated or recognized from Yang *et al.* the feature thought to be inherent, namely, that dimers and multimers could be separated from their own monomers, let alone the minimum yields or purity levels stated. As mentioned above, there are chromatographic media designed specifically to separate proteins by size (size-exclusion chromatography) and these were used by practitioners before June 1998 to achieve the separation of monomers from their dimers and/or multimers as claimed. The skilled practitioner would not have recognized that monomers could be separated to the level of purity and yields claimed; evidence to the contrary is shown by the fact that such ion-exchange purification methods were not used to purify monomers from their dimers and/or multimers before the present invention was made, but rather size-exclusion chromatography.

Since Yang *et al.* do not contain the supporting data or text describing separation of monomers from their dimers and/or multimers, the skilled practitioner, without the teachings disclosed for the first time by the present application, would not have recognized that separation of monomers from their dimers and/or multimers at such

high yields and purity would be possible using the claimed method of purification.

In view of the foregoing, this rejection of claims 1-2, 5-7, and 9-13 based upon Yang *et al.* under 35 U.S.C. §102(b) should be withdrawn and applicants so request reconsideration and withdrawal thereof.

Claims 1, 2, 5, and 8-13 are rejected under 35 USC §102(a) as being anticipated by Hahn *et al.*, Chromatography, 795, 277-287 (1998).

The Examiner urges that Hahn *et al.* teach elution of the IgG monomers from a mixture (bovine whey) which contains monomers and dimers or multimers, and thus is directly applicable to the present claims. According to the Office, applicants have provided no evidence to support their assertion that the mixture taught in Hahn *et al.* does not contain dimers and/or multimers.

Applicants refer to the test of anticipation set forth above with respect to Yang *et al.* First, all of the elements and features of the claimed invention are not set forth in Hahn *et al.*, since the claims require that the monomer be separated from **its own** dimers and/or multimers. While the bovine whey may well contain dimers and multimers, Hahn *et al.* provides no explicit or implicit disclosure that the polypeptide monomer being purified from the bovine whey is separated from **its own** dimers and/or multimers, as required by the instant claims. There is further no evidence that such dimers and/or multimers are even present in the bovine whey.

In point of fact, Hahn *et al.* teach separation of various different proteins **from each other**, all of which are contained in bovine whey, such as IgG from lactoferrin and from lactoperoxidase (see, e.g., Table 1 on page 280). There is no evidence in Hahn *et al.* that any separation has occurred between the monomer and any of its own

dimers and/or multimers present in the mixture, as required by the present claims, as opposed to dimers and/or multimers that may naturally be present in bovine whey. In support, see paragraph 9 of the Cramer Declaration.

Further, Hahn *et al.* do not anticipate the instant invention by inherency. As noted above, to establish inherency, the inherent characteristic must **necessarily** be present in the prior art reference **and** such characteristic would have to have been **recognized** by a person of ordinary skill in the art at the time. Hahn *et al.* satisfy neither of these requirements.

First, Dr. Cramer in paragraph 10 of the enclosed Declaration refutes the assertion that Hahn *et al.* teach purification of immunoglobulins using an identical method to that instantly claimed and that purification in Hahn *et al.* would thus include elution of the IgG monomers from a mixture (bovine whey) that contains monomers and dimers or multimers. He notes that, as established above, the separation of monomers from dimers and/or multimers thereof (the characteristic of the claimed invention deemed to be inherent) is not **necessarily** or actually achieved by practicing the ion-exchange technique with the protein load mixture used by Hahn *et al.* to purify immunoglobulins from bovine whey. The ordinarily skilled scientist versed in purification techniques would not have reasonably concluded from the teachings of Hahn *et al.* that purification of monomers from their dimers and/or multimers would be feasible in June 1998. Since the inherent characteristic does not necessarily flow from Hahn *et al.*, Hahn *et al.* does not anticipate the present invention.

Second, one of ordinary skill in the art at the time of the present invention must have appreciated or recognized the inherent feature, namely, that dimers and multimers could be separated from their own monomers, to establish inherency. This issue is addressed

by paragraph 11 of the Cramer Declaration, wherein he states that the skilled scientist in chromatography would not have appreciated or recognized as of June 1998 from Hahn *et al.* that monomers could be separated from their dimers and/or multimers. Since Hahn *et al.* do not contain the requisite teachings, the skilled scientist would not have recognized that separation of monomers from their dimers and/or multimers would be possible using the claimed method of purification.

Further, in paragraph 12, Dr. Cramer addresses the purity of the mixture obtained in Hahn *et al.* Specifically, he notes that Hahn *et al.* obtain mediocre results upon purification of IgG from other whey proteins (not from its dimers/multimers). In all lanes of the SDS-PAGE gels of Fig. 4 IgG co-elutes with at least one of the other whey proteins. One skilled in this field would conclude from this figure that the separations were not optimal for the purification of IgG from whey proteins, and none achieved close to the 99.5% purity shown in the Examples of the above application, which reflects the separation level of monomer from its own dimers and/or multimers, not just from whey proteins. The authors of Hahn *et al.* include comments such as "[w]hen IgG is eluted from S-Sepharose FF, it co-elutes with beta-lactoglobulin and alpha-lactalbumin" (page 287, par. 2), and "[a] second purification step must be added, if high purity of a certain protein is desired" (p. 287, par. 3), indicating that the method does not achieve optimal purification of any protein, much less a polypeptide monomer from its dimers and/or multimers. Hence, Hahn *et al.* do not disclose the purity recitations set forth in the claims.

Because there is no anticipation by Hahn *et al.* of claim 1, and all other rejected claims depend on claim 1, applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 USC §102(a) over this reference.

Rejections under 35 USC §103

Claims 1-2 and 4-13 are rejected under 35 USC §103(a) as being unpatentable over Yang *et al.* in view of US 4,764,279 (Tayot *et al.*). This rejection is respectfully traversed.

The Examiner contends that the mixture of Tayot is blood and thus would contain dimers and multimers inherently. Further, the Office alleges that one of skill in the art would reasonably expect that a method useful for purifying proteins that is identical in method steps to the instant method would function identically as well, and thus perform the specific purification of monomers from dimers and multimers of the monomer and would result in the same levels of purity that are instantly claimed.

A finding of obviousness under 35 U.S.C. §103 requires a determination of the scope and content of the prior art, the differences between the invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). Other considerations, such as unexpected results, failure of others, *etc.*, that are indicia of non-obviousness must be taken into account, if present. *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 894, 904 (Fed. Cir. 1988). Once the scope and content of the prior art is determined, the relevant inquiry is whether the prior art as a whole **suggests** the invention, and whether one of ordinary skill in the art would have had a **reasonable expectation** that the claimed invention would be successful. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991) (emphasis added). When references are combined to support a rejection, there must be some teaching in the references themselves that suggests the combination. If an explicit suggestion or teaching is missing from a

reference, it cannot be supplied by an inherent feature to support an obviousness rejection. *In re Sernaker*, 217 USPQ 1 (Fed. Cir. 1983).

Inherency is immaterial in an obviousness analysis if the record establishes that one of ordinary skill in the art would not appreciate or recognize the inherent result. *In re Shetty*, 195 USPQ 753 (C.C.P.A. 1977). That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. *In re Rijckaert*, 28 USPQ 2d 1955 (Fed. Cir. 1993).

Yang *et al.* lack a suggestion of separation of a polypeptide monomer from dimers and/or multimers of such monomer with the minimum purity and yields as claimed. Since the technique utilized by Yang *et al.* is routinely used by those of skill in the art, Yang *et al.* do not even provide the motivation for using ion-exchange to separate monomers from their dimers and/or multimers in the claimed purity and yield levels.

Since Yang *et al.* do not disclose, or even suggest, the claimed invention, one of ordinary skill in the art also would not have had a reasonable expectation that the claimed invention would be successful. More specifically, and contrary to the Examiner's assertions, Yang *et al.* do not disclose the separation of monomers from their dimers and/or multimers in the yield and purity of product as claimed. Yang *et al.* do not show any specific level of yield or purity, much less the minimum 90% yield and 99.5% purity levels that are recited in the claims.

Regarding Tayot *et al.*, the Examiner is directed to paragraph 13 of the Cramer Declaration stating that the claimed invention would not have been obvious as of June 1998 from the combination of Tayot *et al.* with Yang *et al.* Tayot *et al.* do not disclose or suggest how one skilled in the art might separate proteins from their own dimers and/or multimers. Instead, hemoglobin, gamma-globulins, and albumin

are separated from each other and presumably also from other unrelated proteins in the blood (see, e.g., claim 1), or hemoglobin and albumin are separated from each other and presumably also from other unrelated proteins in the blood (see, e.g., claim 10). These protein moieties are not related as monomers and dimers of such monomers and/or multimers of such monomers, as is required in the claimed method of the above application. The anion-exchange step described in Tayot *et al.* is designed such that only albumin binds to the column and the hemoglobin and immunoglobulins flow through the column. The gamma-globulins are separated from the hemoglobin by precipitation in ice-cold ethanol.

Therefore, according to Dr. Cramer in paragraph 13, the purification of IgGs is achieved by a method (precipitation) completely distinct from the presently claimed ion-exchange method (see col. 4, lines 10-54 of Tayot *et al.*). Tayot *et al.* further state that the Ig precipitate "...must then be subjected to other purification operations already known so as to prepare immunoglobulins which may be used in human therapeutics" (col. 4, lines 48-51), just as with albumin (compare col. 4, lines 29-31). It is evident that the anion-exchange method described does not purify the gammaglobulins or albumin from its dimers and/or multimers. These statements regarding further purification that is required actually teach away from the claims of the above application where no further purification step is used.

Further, this combination of references would not have disclosed or suggested the unexpectedly high minimum purity and yield levels claimed by applicants, e.g., greater than 99.5% and greater than 90%, respectively.

Failing to suggest the invention and to provide a reasonable basis for its success, Yang *et al.* in combination with Tayot *et al.* do not meet the standards of obviousness set forth above.

Specifically, one of ordinary skill in the art would not have had a reasonable expectation that the claimed invention would be successful, and there is no teaching in the references themselves that suggests the combination. Without such teaching, an inherent feature fails to compensate for this deficiency. Further, inherency is immaterial in this obviousness analysis because the record establishes that one of ordinary skill in the art would not have appreciated or recognized the inherent result. Obviousness cannot be predicated on what is unknown. Hence, this rejection of claims 1-2 and 4-13 is in error and applicants respectfully request that it be withdrawn.

Claims 1-3 and 5-13 are rejected under 35 USC §103(a) as being unpatentable over Yang *et al.* and Hahn *et al.* in view of the Oncogene Science catalog 1992, pages 18 and 34. The Examiner contends that the catalog pages are cited to teach the desirability of the purification process, i.e., that purified antibodies are commercially desirable.

The Examiner is referred to the legal standards to establish obviousness noted above. The claimed invention would not have been obvious from the Oncogene Science catalog along with Yang *et al.* and/or Hahn *et al.* Dr. Cramer notes in paragraph 14 of his Declaration that the latter references contain no details or directions to instruct the skilled artisan on how to obtain pure antibodies from impure mixtures containing dimers and multimers of the antibody monomers to be separated for the reasons noted above. Further, the so-called highly purified antibodies of the catalog are actually only research-grade material, so that their level of purity has no bearing on the level of purity needed to obtain antibodies suitable for therapeutic needs, as the claimed level of greater than 99.5% reflects. Such antibodies are much more highly purified than research-grade antibodies.

In fact, neither Yang *et al.* nor Hahn *et al.* nor the Oncogene Science catalog even acknowledge the existence of dimers and/or multimers of polypeptide monomers, let alone that a separation thereof from the monomers can occur so as to obtain highly pure monomeric antibodies. The combined references would not have suggested the claimed invention as set forth above, particularly with the purity and yield results. See paragraph 14 of the Declaration of Steven Cramer in this regard.

Hence, reconsideration and withdrawal of the rejection of claims 1-3 and 5-13 under 35 USC §103(a) as being unpatentable over Yang *et al.* and Hahn *et al.* in view of the catalog is respectfully requested.

Further evidence of unobviousness

In paragraph 15 of the Cramer Declaration he provides further evidence to rebut both obviousness rejections. Specifically, when he first heard about the invention claimed in the above application, he was surprised that the technique could be used to separate monomers from their own dimers and/or multimers at such unexpectedly high minimum purity and yield levels obtained as claimed, i.e., greater than 99.5% and greater than 90%, respectively. Size-exclusion chromatography was the gold standard at the time for distinguishing between these very similar protein species. His colleagues and he working in the separation arts would not have expected from Yang *et al.* combined with Tayot *et al.* or from Yang *et al.* and Hahn *et al.* in combination with the selected catalog pages that such a high yield and purity could be achieved.

There is thus nothing in the collection of references that would have motivated the skilled artisan to purify the polypeptide monomers from their dimers and multimers to the claimed purity and yield levels using the claimed method at the priority date.

Summary

Dr. Cramer summarizes the evidence supporting patentability of the claimed invention in paragraph 16 of his Declaration. Namely, he states that the above citations alone or in combination merely disclose that proteins can be purified to some degree using ion-exchange chromatography. In particular, the disclosures clearly show separation of IgG from BSA or IgG partially separated from whey, serum, or ascites proteins, *etc.* None of the cited references even mentions the existence of dimers and/or multimers of polypeptide monomers. Nowhere do these references, alone or in combination, mention or suggest the separation of monomers from their dimers/multimers using ion-exchange chromatography as claimed, much less with the claimed yield and purity results. Such results would not have necessarily followed from practicing the teachings of these references due to the nature of the mixtures being loaded on the column in these references, and the skilled practitioner would not have appreciated or expected from these teachings that such could be done.

Information Disclosure Statement

On September 1, 1999 applicants mailed to the USPTO an Information Disclosure Statement citing references 1-11. A postcard receipt indicates that the USPTO received this paperwork on September 7, 2001. During a telephone conference with the Examiner in August, 2001 the undersigned attorney learned that the USPTO does not have a record of this IDS. The Examiner suggested that another copy be sent to the USPTO with this Amendment. Therefore, a copy of this paperwork is enclosed. Also, on July 26, 2000 applicants mailed to the USPTO a Second Supplemental Information Disclosure Statement citing three more references (16-18), which the Examiner appears to have in the file. However, applicants do not have this initialed form either.

**Therefore, applicants respectfully request that the PTO-1449 forms listing references 1-11 and 16-18 be initialed and returned to applicants for their records.**

It is believed that all claims are in condition for allowance, and a notice to that effect is earnestly solicited. If the Examiner has any questions, she should feel free to call the undersigned attorney at the number indicated below.

Respectfully submitted,
GENENTECH, INC.

Date: September 11, 2001

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